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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,678	KAYED ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *181-206* is/are pending in the application.

4a) Of the above claim(s) *192 and 193* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *181-191,194-206* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 29 September 2008 has been received and entered in full. Claims 1-180 were cancelled per amendment of 11 March 2005. Claims 181-184 and 186-192 have been amended. New claims 194-206 have been added. Note: Attention is hereby drawn to state that although Applicant states that new claim 207 is added (see page 6, lines 3 and 6 of Remarks dated 29 September 2008), there is no new claim 207 in the amendment. It is not clear whether this is a typo or was inadvertently missed out from the amended claim listing.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 181-191 drawn to a composition comprising an isolated conformational epitope of an amyloid aggregate which forms in an animal or a human and which contributes to amyloid disease formation, in the reply filed on 29 September 2008 is acknowledged.

3. Claims 192-193 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 29 September 2008.

4. Claims 181-191 and 194-206 are under consideration in the instant application.

Drawings

5. The drawings are objected to because:

Figures 3, 4, and 6-9 do not have a figure legend having the signs corresponding to high and low molecular weights Aβ and Aβ fibrils.

6. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

7. The disclosure is objected to because of the following informalities:

Internet address:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, page 12, line 5). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Objections

8. Claims 184, 186, 205 are objected to because of the following informalities:

i) Claim 184 recites non-elected inventions.

ii) Claim 186 has the wrong claim status “Previously Presented”, instead of the correct “Presently Amended”.

iii) Claim 205 depends from a non-existent claim 217.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 181-183, 191, 199, are rejected under 35 U.S.C. 102(a) as clearly anticipated by Tjernberg et al., (Biochem J. 366: 343-351, 2002).

10. The claims are drawn to a composition comprising an isolated conformational epitope of an amyloid aggregate that forms in a human or animal and contributes to amyloid disease, wherein the composition comprises a peptide and the epitope is conformationally constrained, is an Aβ amyloid epitope and is a toxic species of an amyloid aggregate.

11. Tjernberg et al. teach conformationally constrained peptides in solution comprising Aβ fragments necessary for aggregation and fibril formation (abstract; Introduction, para 1; page 345, col 2, para 1). The reference further teaches that

the polymerization of the amyloid fibrils results in the pathogenesis of amyloid diseases like Alzheimer's Disease, therefore, is neurotoxic (page 349, col 1, para 4; Introduction, para 1). Since the amyloid peptides of the reference are purified during processing (page 345, col 2, para 1), the peptides are isolated by definition in the instant specification that states that isolated means "purified, substantially purified or partially purified" (para 0046). Thus the composition of the reference anticipates the invention.

12. Claims 181-182, 191 are rejected under 35 U.S.C. 102(b) as anticipated by Prusiner et al., (US PGPUB No. 20010014455 A1, dated 16 August 2001).

13. Prusiner et al. teach a sample comprising a protein comprising disease conformation that binds to an antibody for detection, thereby inherently having the conformational epitope of the protein. The reference further teaches that the protein is an amyloid protein, (prion protein scrapie isoform) (abstract). Thus the composition of the reference anticipates the invention.

14. Claims 181-183, 191, 199, are rejected under 35 U.S.C. 102(e) as anticipated by Solomon et al., (US Patent No. 6703015, filed 29 December 1999).

15. Solomon et al. teach pharmaceutical composition comprising an active ingredient comprising an epitope of an aggregating protein, or beta amyloid (abstract) with plaque formation in a plaque forming disease. The reference further teaches that the epitope can be formed from contitguous or non-contiguous amino acids juxtaposed by tertiary folding of a protein (col 17, lines 12-14), therefore, inherently teach compositions comprising a conformational epitope. Thus the composition of the reference anticipates the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of

35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 181-185, 189, 191, 195, 199, 203-206 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjernberg et al., (Biochem J. 366: 343-351, 2002) OR, Solomon et al. (US Patent No. 6703015, filed 29 December 1999), in view of Garzon-Rodriguez et al. (JBC 275: 22645-22649, 2000), and further as evidenced by Goyal et al. (International Application Publication No, WO9707403 A1, dated 27 February 1997), and Wolf et al. (The Embo Jour 9: 2079-2084, 1990).

18. The claims are drawn to a composition comprising an isolated conformational epitope of an amyloid aggregate that forms in a human or animal and contributes to amyloid disease, wherein the composition comprises a peptide and the epitope is conformationally constrained, is an Aβ amyloid epitope of SEQ ID NO: 2 and is a toxic species of an amyloid aggregate (claims 181-184, 191, 199). The claims further recite that the aggregate has a molecular weight of 1kDa to about 100000000 kDa, and that the C-terminus of the peptide epitope is bound to the surface (claims 189, 195), wherein the surface is flat or comprises a pleated sheet or is a protein (claims 203-206).

19. The teachings of Tjernberg et al or Solomon et al. are set forth above.

20. Tjernberg et al. or Solomon et al. do not teach that the C-terminal end of the amyloid peptide is bound to the surface.

21. Garzon-Rodriguez et al. teach that the carboxyl terminal residues of Aβ peptides constitute a richly hydrophobic domain that is associated with the cell membrane. The reference also teaches that the carboxyl terminal is critical for the assembly dynamics of amyloid. Still further Garzon-Rodriguez et al. teach that the amyloid fibril has a β pleated sheet structure (page 22645, Introduction). It is well established that the amyloid fibrils are formed by the sequential addition of Aβ subunits, thereby teaching that the amyloid peptides having epitopes for aggregate formation are bound to the amyloid fibril. It is further evidenced that the β- or A4 amyloid protein having 100% sequence homology with the instantly claimed SEQ ID NO: 2 (Goyal et al. abstract; see Appendix A for SCORE alignment) aggregates in the brain of AD patients. It is also well established in the literature that amyloid protein subunits associated with disease forming aggregates have a molecular weight of 4.2-4.5 kDa (Wolf et al. page 2079, para 1).

22. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the composition comprising conformationally constrained peptides comprising Aβ fragments necessary for aggregation and fibril formation of Tjernburg et al. or Solomon et al. by constraining the C-terminus of the amyloid peptide epitope to the surface of the membrane as taught by Garzon-Rodriguez et al. The person of ordinary skill in the art would have been motivated to bind the C-terminus residues to the surface, as the conformation change coincident with dimer to fibril formation

takes place in the carboxyl terminus region of the amyloid peptide (Garzon-Rodriguez et al., abstract; page 22649, concluding para) resulting in aggregation, and because the aggregation of Aβ is a critical factor for pathogenesis (page 22645, col 2, para 1). The person of ordinary skill in the art would have expected success because conformation structure analysis was conducted while designing therapeutics for AD and other diseases at the time the invention was made.

23. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

24. Claims 181-185, 189, 191, 195, 196, 199, 203-206 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjernberg et al., (Biochem J. 366: 343-351, 2002) OR, Solomon et al. (US Patent No. 6703015, filed 29 December 1999), in view of Garzon-Rodriguez et al. (JBC 275: 22645-22649, 2000), and further in view of Ingenito et al. (J. Am Chem Soc 121: 11369-11374, 1999).

25. Claim 196 further recites that the C terminus is bound to the surface by a carboxy thiol linkage.

26. The teachings of Tjernberg et al, Solomon et al, and Garzon-Rodriguez et al. are set forth above.

27. Tjernberg et al., Solomon et al. or Garzon-Rodriguez et al. do not teach that the C terminus is bound to the surface by a carboxy thiol linkage.

28. Ingenito et al. teach peptide synthesis by linking a thiol to generate peptide-C-terminal thioesters (abstract).

29. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the composition comprising conformationally constrained C-terminus peptides comprising Aβ fragments of Tjernburg et al., Solomon et al. and Garzon-Rodriguez et al., by having a thiol linkage at the carboxyl end as taught by Ingenito et al. The person of ordinary skill in the art would have been motivated to link a thiol group, because the displacement with a suitable thiol at the C-terminus end produces peptide thioesters with much higher yields and is a reproducible method for the synthesis of proteins with backbone-engineered structure (page 11369, abstract; para 1). For example, the cleavage of peptide from resin where the protein is bound is much more effective in C-terminal thioesters than in other groups (Ingenito et al. Table 1).The person of ordinary skill in the art would have expected success because peptide C-terminal thioesters have been successfully used for peptide synthesis at the time the invention was made.

30. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

31. Claims 181-183, 185, 187, 190, 191, 194, 204, are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjernberg et al., (Biochem J. 366: 343-351, 2002) OR, Solomon et al. (US Patent No. 6703015, filed 29 December 1999), in view of Nordstedt et al (US Patent No. 6331440, dated 18 December 2001).

32. The claims further recite that the composition comprising an isolated conformational epitope of an amyloid aggregate is constrained on a flat surface wherein the composition or the epitope is chemically bound to the surface, and wherein the epitope comprises 5 or more monomers (claims 185, 187, 190, 194).

33. The teachings of Tjernberg et al and Solomon et al. are set forth above.

34. Tjernberg et al. or Solomon et al. do not teach the surface specifications or that the amyloid comprises 5 or more monomers.

35. Nordstedt et al teach the synthesis of ten-mers corresponding to consecutive sequences of Aβ 1-40 on a filter matrix, wherein the peptides are coupled to cellulose membranes using 2 molecules of β alanine as spacer (col 5, lines 52-57), i.e. the peptides are chemically bound to the membrane.

36. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the composition comprising conformationally constrained peptides in solution comprising Aβ fragments necessary for aggregation and fibril formation as taught by Tjernburg et al. and Solomon et al. by making ten-mer amyloid aggregate coupled or constrained onto a membrane surface as taught by Nordstedt et al. The person of ordinary

skill in the art would have been motivated to have a composition comprising 5 or more monomers of amyloid peptide because the disease associated amyloid consists of thin fibrils of polymerized Aβ, and a rational pharmacological approach for the prevention of amyloidogenesis would involve interference with Aβ polymerization. The person of ordinary skill in the art would have expected success because synthesis of peptide or Aβ polymers chemically bound on flat membrane is a routine technique in pharmaceutical laboratories, and was being performed in pharmaceutical and research laboratories at the time the invention was made.

37. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

38. Claims 181-186, 188, 189, 191, 195-206 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjernberg et al., (Biochem J. 366: 343-351, 2002) OR, Solomon et al. (US Patent No. 6703015, filed 29 December 1999), Garzon-Rodriguez et al. (JBC 275: 22645-22649, 2000), and Ingenito et al. (J. Am Chem Soc 121: 11369-11374, 1999), and further in view of Braun (US PGPUB No. 20030185835 A1, filed 19 March 2002).

39. Claims 185-186, 188, 195-198, 200-202 recite that the epitope is constrained on a curved/flat surface or on a surface of a particle on a support surface comprising a metal or mixtures thereof, e.g. gold or colloidal gold.

40. The teachings of Tjernberg et al, Solomon et al., Garzon-Rodriguez et al. and Ingenito et al. are set forth above.

41. Tjernberg et al., Solomon et al., Garzon-Rodriguez et al. or Ingenito et al. do not teach the surface specifications of a particle coated with a metal or gold.

42. Braun teaches the administration of pharmaceutical preparations or compositions comprising the antigen. Specifically, Braun teaches that the antigen is coated onto a surface of carrier particles of colloidal gold (para 0414). Since the particle is spherical (para 0431), it would inherently have a curved surface.

43. Braun does not teach that the epitope of amyloid aggregate is conformationally constrained C-terminus of a peptide having a thiol linkage on a particle.

44. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the composition comprising conformationally constrained C-terminus peptides having a thiol linkage comprising Aβ fragments necessary for aggregation and fibril formation as taught by Tjernburg et al., Solomon et al., Garzon-Rodriguez et al. or Ingenito et al. by constraining onto colloidal gold particles as taught by Braun. The person of ordinary skill in the art would have been motivated to use gold for constraining the conformational epitopes of amyloid because gold provides uniformity of size in a range of particle sizes with suitable density, appropriate for intracellular delivery and reduced toxicity (Braun, para 0414-0415). The person of ordinary skill in the art would have expected success because synthesis of constrained

conformational epitopes on gold surface was being performed in pharmaceutical and research laboratories at the time the invention was made.

45. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

46. No claims are allowed.

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is 571-272-90379037. The examiner can normally be reached on M-F.

48. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

49. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
14 December 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649